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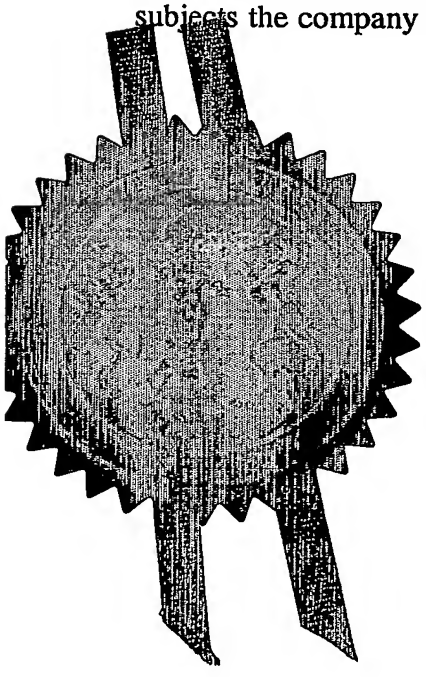

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Dated 10 December 2003

Patents Form 1/77

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P01/7700 0.00-0310472.6

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The Patent Office

Cardiff Road
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NP9 1RH

1. Your reference — REP07230GB

2. Patent application number *(The Patent Office will fill in this part)* — 0310472.6 — 7 MAY 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Amedis Pharmaceuticals Ltd
Unit 162
Cambridge Science Park
Milton Road
Cambridge
CB4 0GP

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

8576993001

4. Title of the invention — COMPOUNDS AND THEIR USE

5. Name of your agent *(if you have one)* — Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)* — 745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	17
Claim(s)	2
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date
7 May 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry
020 7377 1377

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COMPOUNDS AND THEIR USE

Field of the Invention

This invention relates to compounds and their use in therapy.

Background to the Invention

Gonadotropin-Releasing Hormone (GnRH) plays a key role in the biology of reproduction. GnRH is also known as luteinizing hormone-releasing hormone (LH-RH).

The GnRH decapeptide (pyro-Glu-His-Trp-Ser-Tyr-Gly-Leu-Art-Pro-Gly-NH_2 or p-EHWSYGLRPG-NH_2) is formed in neurons of the medical basal hypothalamus from a larger precursor via enzymatic processing. The peptide is released in a pulsatile manner into the pituitary portal circulation system, where GnRH interacts with high-affinity receptors (7-transmembrane G-protein coupled receptors) in the anterior pituitary gland located at the base of the brain. Here, GnRH triggers the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are gonadotropic hormones (gonadotropins). LH stimulates the production of testosterone and estradiol in the testes and ovaries respectively, whilst FSH stimulates follicle growth in women and sperm formation in men. When correctly functioning, the pulsatile release and concentration levels of GnRH are critical for the maintaining of gonadal steroidogenesis and for normal functions of reproduction related to growth and sexual development.

The pituitary response to GnRH varies greatly throughout life. GnRH and the gonadotropins first appear in the foetus at about ten weeks of gestation. Sensitivity to GnRH reduces until the onset of puberty. There is, however, a brief rise during the first three months after birth. Prior to puberty, the FSH response to GnRH is greater than that of LH. Once puberty begins, sensitivity to GnRH increases, and pulsatile LH secretion ensues. Later in puberty and throughout the reproductive years, pulsatile release of GnRH occurs throughout the day, with responsiveness to LH being greater than that of FSH. Pulsatile GnRH release results in pulsatile LH and FSH release and thus testosterone and estradiol release from the gonads. Post-menopause, the concentration of FSH an LH rise, and the post-menopausal levels of FSH are higher than those of LH.

Chronic administration of GnRH agonists and antagonists results in decreased circulating levels of both LH and FSH. GnRH agonists are compounds that mimic endogenous GnRH to stimulate receptors on the pituitary gland, resulting in release of LH and FSH. After a transient rise in gonadal hormone production ("flare" response), the chronic administration of GnRH agonists results in down-regulation of the GnRH receptors. This down-regulation and desensitization results in a reduction in the circulating levels of LH and FSH. In spite of the symptom-exacerbating hormonal flare experienced, GnRH agonists have been the preferred treatment for sex-steroid-dependent pathophysiologies. GnRH agonists have been used to reduce testosterone production, thereby reducing prostate volume in benign prostatic hyperplasia (BPH) and slowing tumour growth in prostate cancer. Such compounds have also been used in the treatment of breast and ovarian cancers.

In recent years, GnRH antagonists have become available for clinical evaluation, and have been shown to have an immediate effect on the pituitary but without the observed flare associated with agonists. Use of GnRH antagonists has been reported for the treatment of ovarian, breast and prostate cancers.

Other uses of antagonists include endometriosis (including endometriosis with pain), uterine myoma, ovarian and mammary cystic diseases (including polycystic ovarian disease), prostatic hypertrophy, amenorrhea (e.g. secondary amenorrhea), and precocious puberty. These compounds may also be useful in the symptomatic relief of premenstrual syndrome (PMS). Antagonists may also be useful to regulate the secretion of gonadotropins in male mammals to arrest spermatogenesis (e.g. as male contraceptives), and for treatment of male sex offenders. GnRH antagonists and agonists have been shown to have utility in treatments where a reversible suppression of the pituitary-gonadal axis is desired.

The presence of GnRH receptors on anterior pituitary cells and several tumour cell types offers the opportunity to develop drugs that act upon receptors to treat both hormone-dependent and hormone-independent cancers.

Conventionally, androgen deprivation has been the most effective systematic therapy for the treatment of metastatic carcinoma of the prostate. The prostate gland requires androgens for normal growth, maintenance, and function. Prostate cancer and benign prostate hyperplasia, however, are common in men and develop in an environment of continuous exposure to androgen. Utilizing a GnRH antagonist to interrupt the pituitary-gonadal axis reduces androgen production and results in tumour growth modulation.

GnRH antagonists may have a direct effect on tumour growth by blocking receptors on the tumour cells. For those cancer types that respond both to sex hormones and to GnRH directly, antagonists should be effective in slowing tumour growth by two mechanisms. Since GnRH receptors are present on many prostate and breast cancer cells, it has recently been proposed that GnRH antagonists may also be effective in treating non-hormone-dependent tumours. Recent literature examples indicate that GnRH receptors are present on a number of cancer cell lines. In particular, prostate, ovarian and breast cancers (see for example Montagnani *et al*, *Arch. Ital, Urol. Androl.* **1997**, *69(4)*, 257-263; Jungwirth *et al.*, *Prostate* **1997**, 32(3), 164-172; Srkalovic *et al* ., *Int. J. Oncol.* **1998**, *12(3)*, 489-498; Kottler *et al.*, *Int. J. Cancer* **1997**, *71(4)*, 595-599.

Available GnRH antagonists have primarily been peptide analogues of GnRH (see, for example, WO93/03058). Peptide antagonists of peptide hormones have some potency but, the use of current peptide antagonists is often associated with problems because peptides are degraded by physiological enzymes and often poorly distributed within the organism being treated. They thus have a limited effectiveness as drugs.

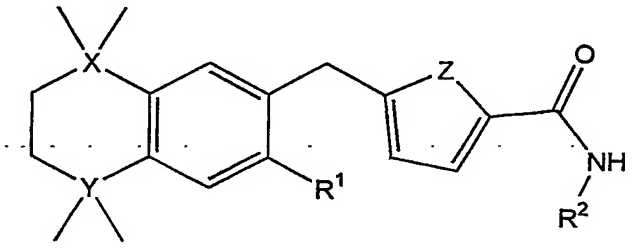
WO00/20358 discloses non-peptide analogues of GnRH.

Sila-substitution (C/Si-exchange) of drugs is a relatively recent approach for searching for organosilicon compounds which have beneficial biological properties. The approach involves the replacement of specific carbon atoms in compounds by silicon, and monitoring how the biological properties of the compounds have changed. A review of this approach is provided in Tacke and Zilch, Endeavour, New Series, 10, 191-197 (1986).

Summary of the Invention

The present invention concerns small-molecule non-peptidic GnRH antagonists that exploit both of the above-described mechanisms of action. Such non-peptidic agents may have advantageous physical, chemical and biological properties compared to peptides, and may be useful as medicaments for diseases such as those mediated via the pituitary-gonadal axis and by directly targeting the receptor on tumour cells.

According to a first aspect of the invention, a compound has the formula (I)



(I)

wherein

one of X and Y is Si and the other is C or Si;

Z is N(R), O or S, wherein R is H or alkyl;

R^1 is H, halogen, alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl; and

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl or -alkyl-heteroaryl;

or a pharmaceutically acceptable salt thereof.

Compounds of the invention are GnRH antagonists. Accordingly, another aspect of the invention is the use of a compound of formula (I) for the manufacture of a medicament for the treatment or prevention of a disease or condition associated with GnRH. The compounds may have utility in the treatment or prevention of a fertility disorder, or in cancer therapy.

Another aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable diluent or carrier, for use in therapy.

The compounds may provide better biodistribution and tolerance to degradation by physiological enzymes, and are thus pharmaceutically advantageous over peptide compounds.

Description of the Invention

Certain compounds and combinations of substituents are preferred; in particular see the subclaims.

Preferred compounds of the invention include those wherein R^1 is H or alkyl, preferably methyl or ethyl, and/or R^2 is aryl, preferably substituted aryl.

The term "alkyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like. "C_{1-6} alkyl" has the same meaning. The group may be optionally substituted with hydroxy, halogen and the like.

The term "alkenyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one double bond, of either E or Z stereochemistry where applicable. This term includes for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2- methyl-2-propenyl etc. "C_{2-6} alkenyl" has the same meaning. The group may be optionally substituted with hydroxy and the like.

The term "alkynyl" as used herein refers to an optionally substituted straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one triple bond. "C_{2-6} alkynyl" has the same meaning. The group may be optionally substituted with hydroxy and the like.

The term "aryl" as used herein refers to optionally substituted aromatic ring systems comprising six to ten ring atoms, and optionally substituted polycyclic ring systems having two or more cyclic rings at least one of which is aromatic. This term includes for example, phenyl and naphthyl. The group may be optionally substituted with the substituents being the same or different in each occurrence and selected from halogen, alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, silyloxy, amino, nitro, sulfhydryl, alkylthio, amido, phosphoryl, phosphonate, phosphino, carbonyl, carboxyl, carboxamido, alkylsilyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, ester, heteroalkyl, cyano, guanidine, amidine,

acetal, ketal, amine oxide, aryl, heteroaryl, arylalkyl, heteroarylalkyl, carbamate, hydroxamic acid, imido, sulfonamido, thioamido, thiocarbamate, urea and thiourea.

The term "cycloalkyl" as used herein refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The group may be optionally substituted by any substituent described herein.

The term "heterocycloalkyl" as used herein refers to a saturated heterocyclic moiety having from four to seven carbon atoms and one or more heteroatoms selected from the group N, O, S and includes for example azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl and the like. The group may be optionally substituted by any substituent described herein.

The term "heteroaryl" as used herein refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from O, N and S and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like. The group may be optionally substituted by any substituent described herein.

The term "alkoxy" as used herein refers to an optionally substituted straight chain or branched chain alkoxy group containing between one and six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy and the like. "C_{1-6} alkoxy" has the same meaning. The group may be optionally substituted with halogen and the like.

The term "halogen" as used herein refers to F, Cl, Br or I.

A compound of the invention may be in a protected form. Compounds of the invention may be chiral. They may be in the form of a single enantiomer or diastereomer, or a racemate.

The compounds of the invention may be prepared in racemic form, or prepared in individual enantiomeric form by specific synthesis or resolution as will be appreciated in the art. The compounds may, for example, be resolved into their enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid followed by fractional crystallisation and regeneration of the free base. Alternatively, the

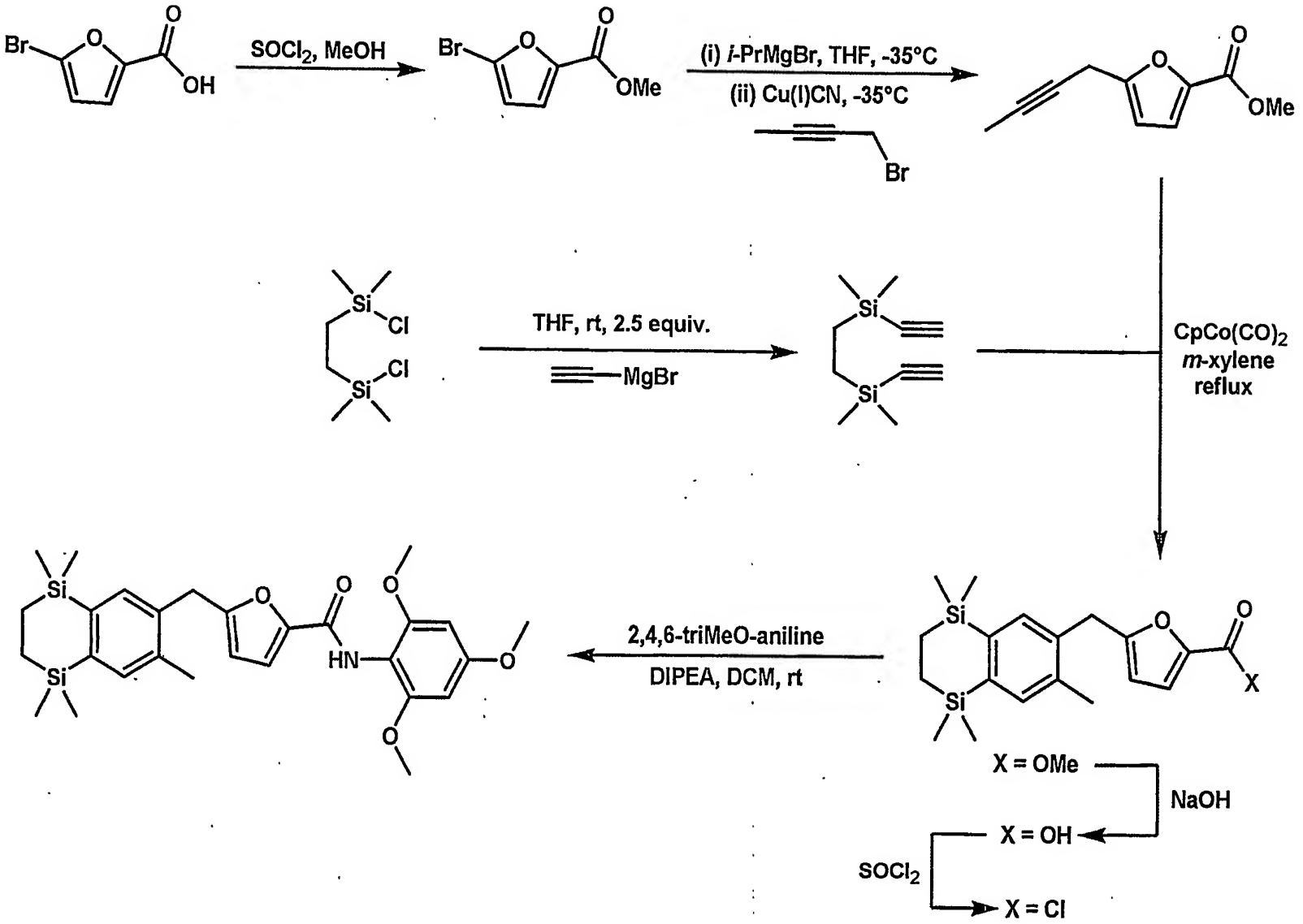
enantiomers of the novel compounds may be separated by HPLC using a chiral column.

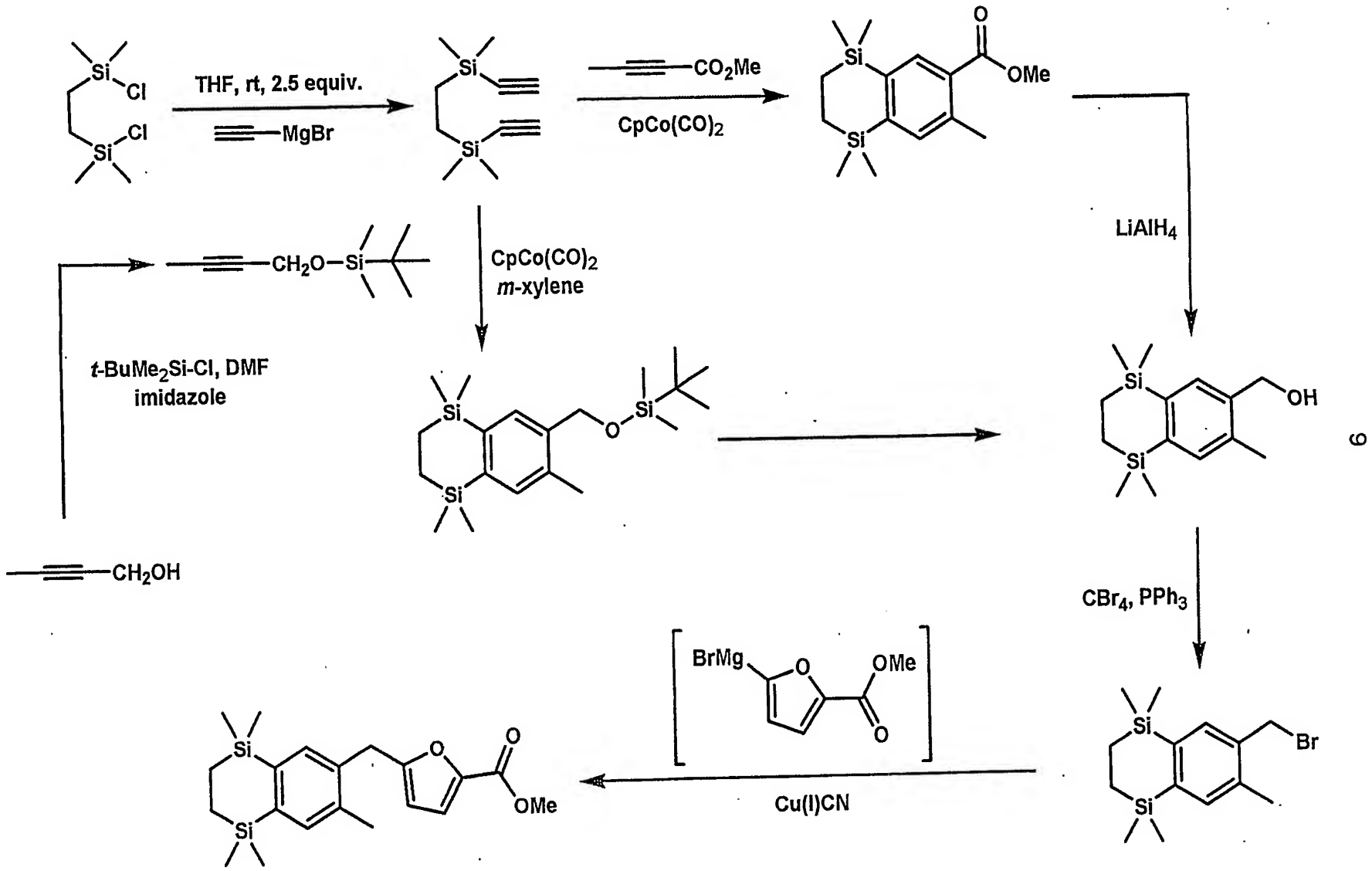
Compounds of the invention may be in the form of pharmaceutically acceptable salts, for example, addition salts of inorganic or organic acids. Such inorganic acid addition salts include, for example, salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, 1,2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, 4-hexylresorcinol, hippuric acid, 2-(4-hydroxybenzoyl)benzoic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphuric acid, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulphuric acid, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ((4-aminophenyl)phosphonic acid), picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid and the like.

Salts may also be formed with inorganic bases. Such inorganic base salts include, for example, salts of aluminium, bismuth, calcium, lithium, magnesium, potassium, sodium, zinc and the like. Organic base salts include, for example, salts of N, N'-dibenzylethylenediamine, choline (as a counterion), diethanolamine, ethanolamine, ethylenediamine, N,N'-bis(dehydroabietyl)-ethylenediamine, N-methylglucamine, procaine, tris(hydroxymethyl)aminoethane ("TRIS") and the like.

As used hereinafter, the term "active compound" denotes a compound of formula (I) including pharmaceutically acceptable salts thereof.

A compound of the invention may be prepared by any suitable method known in the art and/or by the following processes:


Br
O
OH
$SOCl_2$, MeOH
Br
O
OMe
(i) *i*-PrMgBr, THF, -35°C
(ii) Cu(I)CN, -35°C
Br
O
OMe
Si
Cl
Cl
Si
THF, rt, 2.5 equiv.
MgBr
Si
Si
$CpCo(CO)_2$
m-xylene
reflux
Si
Si
O
O
X
X = OMe
NaOH
X = OH
$SOCl_2$
X = Cl
2,4,6-triMeO-aniline
DIPEA, DCM, rt
HN
O
O
O
O


THF, rt, 2.5 equiv.
MgBr
CO2Me
CpCo(CO)2
OMe
LiAlH4
CpCo(CO)2
m-xylene
CH2O–Si
t-BuMe2Si-Cl, DMF
imidazole
CH2OH
OH
CBr4, PPh3
Br
BrMg
OMe
Cu(I)CN
OMe

It will be understood that the processes detailed above are solely for the purpose of illustrating the invention and should not be construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by formation of a salt if appropriate or possible under the circumstances.

A preferred compound of the invention is *N*-(2,4,6-trimethoxyphenyl)-5-[(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furan-2-carboxamide.

The activity and selectivity of the compounds may be determined by any suitable assay known in the art; see, for example, Millar *et al*, Neuroscience, 1995, 25, 145-162.

The compounds of the invention may be used in the treatment or prevention of numerous ailments, conditions and diseases including, but not limited thereto, cancer and fertility disorders.

The term "cancer" as used herein refers to any disease or condition characterised by uncontrolled, abnormal growth of cells and includes all known types of cancer, for example cancer of the bladder, breast, colon, brain, bone, head, blood, eye, neck, skin, lungs, ovaries, prostate and rectum; digestive, gastrointestinal, endometrial, hematological, AIDS-related, muscoskeletal, neurological and gynecological cancers; lympomas, melanomas and leukemia.

In therapeutic use, the active compound may be administered orally, rectally, parenterally, by inhalation (pulmonary delivery), topically, ocularly, nasally, or to the buccal cavity. Oral administration is preferred. Thus, the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers

suitable for use in such compositions are well known in the art. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably, a unit dose comprises the active ingredient in an amount of 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions. The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may

be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture

with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid, find use in the preparation of injectables.

The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore

melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compositions for topical administration are also suitable for use in the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as light liquid paraffin, dispersed in a aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil or wax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally.

The following Example illustrates the invention.

In the Example, all ^1H NMR spectra were run at 400 MHz using $CDCl_3$ as solvent. LC-MS spectra were run using Conditions A1, A2 or B .

Conditions A1 and A2: mass spectrometer - electrospray source operating in positive and negative ion mode. System running at 1.5 ml/min, detection mode is through a Hexa-pole Mass Spectrometry detector and a Diode-Array detector for UV.

Mobile phase: acetonitrile-water (running from 5 – 95% acetonitrile) with either 0.05% formic acid (Conditions A1) or 0.05% ammonium hydroxide (Conditions A2) added.

Conditions B; mass spectrometer - electrospray source operating in positive and negative ion mode. System running at 2.0 ml/min, 200 µl split to the ESI source with inline DAD detection and SEDEX ELS detection.
Mobile phase: (A) Water with 0.1 % formic acid added, (B) acetonitrile with 0.1% formic acid added.

Example: Synthesis of *N*-(2,4,6-Trimethoxyphenyl)-5-[(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furan-2-carboxamide

Step 1. Methyl 5-bromo-2-furoate

To a solution of 5-bromo-2-furoic acid (20g, 0.105 mol) in methyl alcohol (150 ml) was added thionyl chloride (5 ml). The mixture was stirred under an inert atmosphere. After 20 hours, the mixture was evaporated under reduced pressure, co-evaporated with methyl alcohol (2 x 50 ml) and taken up in ethyl acetate (200 ml). This was washed with saturated aqueous sodium bicarbonate solution (50 ml), which was then re-extracted into ethyl acetate (2 x 20 ml). The combined organic phases were dried (using sodium sulphate) and evaporated under reduced pressure to afford the title compound as an off-white amorphous solid that was used as received without further purification (25.8g). ^{1}H NMR δ 7.11 (1H, d, J = 3.5 Hz), 6.44 (1H, d, J = 3.5 Hz) and 3.89 (3 H, s). LC-MS (Conditions A); R_t = 3.43 minutes.

Step 2. Methyl 5-(but-2-ynyl)-2-furoate

A solution of the ester from **Step 1** (1.95 g, 9.56 mmol) in dry tetrahydrofuran (THF, 50 ml) was stirred under nitrogen and cooled to –35°C. To this was added a solution of *iso*-propyl magnesium bromide (15.27 ml, 0.66 M) dropwise over a period of 10 minutes. The reaction was then stirred for 1 hour at -35 °C before copper (I) cyanide (215 mg; 2.42 mmol) and 1-bromo-2-butyne (1.17 ml, 13.38 mmol) were added consecutively and stirring was continued for 1.5 hours. The resulting mixture was then treated with saturated aqueous ammonium chloride solution (25 ml) maintaining the temperature below -30°C before the mixture was allowed to slowly warm to room temperature. The resulting precipitate was removed by vacuum filtration and the solid washed with ethyl acetate (3 x 20 ml). The aqueous phase was separated and extracted into ethyl acetate (3 x 20 ml) before the combined organic phases were dried (using sodium sulphate) and evaporated under reduced pressure. The tan-coloured gum was purified by chromatography (silica, ethyl acetate-petroleum ether; 1:9) to afford the title compound as a pale yellow oil (944 mg, 55% yield). ^{1}H NMR δ

7.13 (1H, d, J = 3.5 Hz), 6.38 (1H, d, J = 3.5 Hz), 3.89 (3H, s), 3.62 (2 H, m) and 1.82 (3H, m). LC-MS (Conditions B); R_t = 3.65 minutes; m/z $[M+H]^+$ 179.

Step 3. Methyl 5-[(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]-2-furoate

A mixture of the ester from **Step 2** (216 mg, 1.2 mmol) and 1,2-bis(ethynyldimethylsilyl) ethane (236 mg, 1.2 mmol; prepared according to Kusumoto et al, *Chemistry Letters*, **1988**, 1149-1152) in dry *m*-xylene (25 ml) was purged with nitrogen (15 minutes) before being heated to reflux under an inert atmosphere. To this boiling mixture was added dicarbonylcyclopentadienylcobalt (11 mg, 0.5 mol%) in dry *m*-xylene (25 ml, solvent also purged with nitrogen before use) via a syringe pump over 9 hours. The reaction was heated overnight before a second solution of the catalyst (0.5 mol%) in *m*-xylene (25 ml) was added drop-wise over a period of 4 hours. The reaction mixture was then allowed to cool, evaporated under reduced pressure and purified by column chromatography (Silica; ethyl acetate-petroleum ether; 1:19) to afford the desired material (112 mg, 25% yield). ^{1}H NMR δ 7.30 (2H, s), 7.12 (1H, d, J = 3.3 Hz), 5.96 (1H, d, J = 3.3 Hz), 4.40 (2H, s), 3.91 (3H, s), 2.29 (3H, s), 0.99 (4H, s), 0.26 (6H, s) and 0.22 (6H, s). LC-MS (Conditions B); R_t = 5.20 minutes.

Step 4. 5-[(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furoic acid

To a solution of the silacycle produced in **Step 3** (200 mg, 0.56 mmol) in ethyl alcohol (20 ml) was added aqueous sodium hydroxide solution (1 M, 0.614 ml) and the mixture was heated to reflux for 2 hours before being concentrated *in vacuo*. Water (25 ml) was added before the resulting mixture was acidified with dilute hydrochloric acid (1 M, to pH 2) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford a tan solid which was purified by flash column chromatography (SiO_2, ethyl acetate-light petroleum; 1:9 containing 1% acetic acid) to afford the desired material (112 mg, 56 % yield). ^{1}H NMR δ 7.32 (2H,

m), 7.10 (1H, d, J = 3.5 Hz), 5.98 (1H, d, J = 3.5 Hz); 3.89 (2H, s), 2.29 (3H, s); 1.01 (4H, s), 0.26 (6H, s) and 0.22 (6H, s).

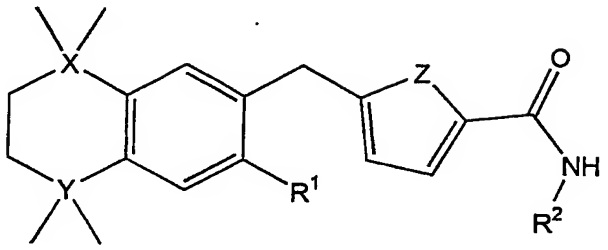
LC-MS (Conditions A1) R_t 4.80 minutes, m/z 359 $[M+H]^+$.

Step 5. *N*-(2,4,6-trimethoxyphenyl)-5-[(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furan-2-carboxamide

To a stirred solution of the acid from **Step 4** (75 mg, 0.209 mmol) in dry dichloromethane (5 ml) under an inert atmosphere was added thionyl chloride (0.076 ml, 1.05 mmol) with continued stirring. After 2 hours a further portion of thionyl chloride (0.5 ml, 6.90 mmol) was added and stirring continued for 3 days. The reaction mixture was evaporated under reduced pressure and co-evaporated with toluene (2 x 10 ml). To a solution of this acid chloride in dry dichloromethane (5 ml) was added diisopropylethylamine (0.18 ml, 1.03 mmol) and 2,4,6-trimethoxyaniline (76 mg, 0.42 mmol). After stirring for 18 hours the reaction mixture was diluted with dichloromethane (25 ml) and washed with hydrochloric acid (1 N, 25 ml). After separation of the two phases the aqueous layer was further extracted with dichloromethane (2 x 10 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (25 ml), which was then re-extracted with dichloromethane (2 x 10 ml). The combined organic extracts were then dried (Na_2SO_4) and evaporated under reduced pressure to give a light tan coloured solid (152 mg) which was purified by column chromatography (silica, 5% methyl alcohol-dichloromethane and then again on silica, 20% ethyl acetate-dichloromethane) to afford the desired product (22 mg, 20% yield) as a solid. ^1H NMR δ 7.36-7.15 (2H, m), 7.08 (1H, m), 6.09 (2H, s), 6.01 and 5.98 (1H, 2 x d, each J = 3.3 Hz), 4.04 and 4.02 (2H, 2 x s), 3.83 (9H, s), 2.35 and 2.33 (total 3H, 2 x s), 0.65-0.72 (2H, m), 0.49-0.55 (2H, m), 0.26 and 0.24 (total 6H, 2 x s) and 0.12 and 0.08 (total 6H, 2 x s). LC-MS (Conditions A1) R_t 4.41 minutes, m/z 524 [M+H]+.

CLAIMS

1. A compound of formula (I)



(I)

wherein

one of X and Y is Si and the other is C or Si;

Z is N(R), O or S, wherein R is H or alkyl;

R^1 is H, halogen, alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl; and

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -alkyl-cycloalkyl, -alkyl-heterocycloalkyl, -alkyl-aryl or -alkyl-heteroaryl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein X and Y are each Si.

3. A compound according to claim 1 or claim 2, wherein R^1 is H or alkyl.

4. A compound according to claim 3, wherein R^1 is methyl.

5. A compound according to any preceding claim, wherein Z is O.

6. A compound according to any preceding claim, wherein R^2 is aryl, $-CH_2$-cycloalkyl, $-CH_2$-aryl, $-CH_2$-heterocycloalkyl or $-CH_2$-heteroaryl.

7. A compound according to claim 6, wherein R^2 is aryl.

8. A compound according to claim 1, which is *N*-(2,4,6-trimethoxyphenyl)-5-[(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]furan-2-carboxamide.

9. A compound according to any preceding claim, for therapeutic use.

10. A pharmaceutical composition comprising a compound of any of claims 1 to 8 and a pharmaceutically acceptable diluent or carrier, for use in therapy.

11. Use of a compound of any of claims 1 to 8, for the manufacture of a medicament for the treatment or prevention of a disease or condition associated with GnRH.

12. Use of a compound of any of claims 1 to 8, for the manufacture of a medicament for cancer therapy.

13. Use of a compound of any of claims 1 to 8, for the manufacture of a medicament for the treatment or prevention of a fertility disorder.